Yogurt consumption in relation to mortality from cardiovascular disease, cancer, and all causes: a prospective investigation in 2 cohorts of US women and men

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ABSTRACT

Background: Although a link between regular yogurt consumption and mortality appears plausible, data are sparse and have yielded inconsistent results.

Objectives: We examined the association between regular yogurt consumption and risk of all-cause and cause-specific mortality among US women and men.

Methods: A total of 82,348 women in the Nurses' Health Study and 40,278 men in the Health Professionals Follow-Up Study without a history of cardiovascular disease (CVD) and cancer in 1980 (women) or 1986 (men) were followed up until 2012. Yogurt consumption was assessed by updated validated FFQs.

Results: During 3,354,957 person-years of follow-up, 20,831 women and 12,397 men died. Compared with no yogurt consumption, the multivariable-adjusted HRs (95% CIs) of mortality were 0.89 (0.86, 0.93), 0.85 (0.81, 0.89), 0.88 (0.84, 0.91), and 0.91 (0.85, 0.98) for ≤1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and >4 servings/wk in women (P-trend = 0.34), respectively. For men, the corresponding HRs (95% CIs) were 0.99 (0.94, 1.03), 0.98 (0.91, 1.05), 1.04 (0.98, 1.10), and 1.05 (0.95, 1.16), respectively. We further noted inverse associations for cancer mortality (multivariable-adjusted HR comparing extreme categories: 0.87; 95% CI: 0.78, 0.98; P-trend = 0.04) and CVD mortality (HR: 0.92; 95% CI: 0.79, 1.08; P-trend = 0.41) in women, although the latter was attenuated in the multivariable-adjusted model. Replacement of 1 serving/d of yogurt with 1 serving/d of nuts (women and men) or whole grains (women) was associated with a lower risk of all-cause mortality, whereas replacement of yogurt with red meat, processed meat (women and men), and milk or other dairy foods (women) was associated with a greater mortality.

Conclusions: In our study, regular yogurt consumption was related to lower mortality risk among women. Given that no clear dose–response relation was apparent, this result must be interpreted with caution. *Am J Clin Nutr* 2020;111:689–697.

Keywords: yogurt, mortality, microbiome, cohort, epidemiology

Introduction

With the recent attention on the gut microbiome, the role of exogenous microbes originating from the diet for improving health has gained renewed interest (1). The complex characteristics of yogurt may confer beneficial health effects by

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Supplemental Table 1 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Data described in the article, code book, and analytic code will be made available upon request pending approval by the investigators of the Nurses' Health Study and the Health Professionals Follow-Up Study.

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Abbreviations used: CVD, cardiovascular disease; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; SFFQ, semiquantitative FFQ.

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providing nutrients such as protein, calcium, magnesium, and vitamin B-12 (2). Moreover, the consumption of commercial probiotic yogurt may modify the intestinal microbiota composition by increasing the diversity of the target probiotic strains (3). Results from experimental studies suggest that commensal microbiota in yogurt such as *Lactobacillus* and *Bifidobacterium* may beneficially affect immune function, which may protect against development of major chronic diseases (4).

A recent study (5) exploring the short-term effect of dietary yogurt consumption, rather than the more concentrated dietary administration of probiotics, on human gut microbiota reported that daily yogurt consumption induced specific changes in bacterial composition and structure in healthy subjects, suggesting that regular yogurt consumption may influence the gut microbiome. However, the beneficial effects of yogurt may not be restricted to the bacteria and their quantity and diversity but may also relate to their metabolic products, e.g., SCFAs.

In epidemiologic studies, including our own data, regular yogurt intake has been linked to lower risks of cardiovascular disease (CVD) (6), type 2 diabetes (7), and certain cancers (8, 9). However, available data relating yogurt consumption to mortality are sparse and have yielded conflicting results. Previous studies did not use repeated measures of yogurt consumption which may have introduced some degree of exposure misclassification error to their analyses. Moreover, previous studies lack the examination of specific alternative substitutions for yogurt, which is an important limitation because the health effects of increasing yogurt consumption may depend on the alternative foods that are substituted for yogurt.

In the present study, we analyzed data from 2 large ongoing prospective cohorts of US women and men to evaluate whether yogurt consumption is associated with reduced risks of all-cause and cause-specific mortality.

Methods

Study populations

The Nurses' Health Study (NHS) is a prospective cohort study of 121,700 registered nurses from 11 US states who were 30–55 y of age at the start of the study in 1976. The Health Professionals Follow-Up Study (HPFS) includes 51,529 male health care professionals aged 40–75 y in 1986. In both cohorts, participants were mailed questionnaires at baseline and every 2 y thereafter to collect and update information on their medical history and lifestyle factors. Beginning in 1980, a 61-item semiquantitative FFQ (SFFQ) was included in the NHS and in 1984, 1986, and every 4 y since, an SFFQ with ~130 items has been administered. Using the expanded SFFQ employed in the NHS, dietary data were collected every 4 y from the HPFS participants starting in 1986.

Among participants who answered baseline questionnaires, we excluded those who had a history of cancer (except nonmelanoma skin cancer) or CVD at baseline, those with yogurt consumption at baseline, those who left >10 items blank on the baseline SFFQ administered in the NHS and >70 items blank on the SFFQ administered in the HPFS, and participants who reported implausible energy intake amounts (<500 or >3500 kcal/d for women, or <800 or >4200 kcal/d for men). After these exclusions, 82,348 women and 40,278 men were included in the analysis (**Supplemental Figure 1**). The study protocol was approved by the institutional review board at the Brigham and Women's Hospital and the Harvard TH Chan School of Public Health and those of participating registries as required.

Assessment of yogurt consumption

Starting in 1980, participants in the NHS were biennially asked to report how often, on average, they consumed yogurt during the previous year, choosing from response categories of "never or less than once per month" (referred to as "never" afterwards), "1–3 per month," "1 per week," "2–4 per week," "5–6 per week," "1 per day," "2–3 per day," "4–5 per day," and "≥6 per day." The standard serving size for yogurt was 1 cup (i.e., 245 g). From 1994, yogurt consumption was separated into 2 items, "yogurt (plain or with NutraSweet)" and "flavored yogurt (without NutrSweet)," and from 2004, items were "plain yogurt," "sweetened yogurt," and "artificially sweetened yogurt." We summed up the single items of yogurt consumption to create 1 yogurt variable. We did not include "frozen yogurt" in our analysis of yogurt consumption, which was asked in the questionnaire in combination with "sherbet, sorbet, and low-fat ice cream." For our analysis, we collapsed yogurt intake into 5 categories: never, >0 to ≤1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and >4 servings/wk. The same questions were asked in the HPFS cohort starting in 1986. The reproducibility and validity of these FFQs have been reported in detail elsewhere (10–15). A high validity was reached for yogurt consumption when compared with multiple diet records, with a correlation coefficient of 0.97 (11).

Assessment of covariates

Dietary covariates were assessed every 4 y by questionnaire, and other lifestyle and medical factors were assessed every 2 y. Potential covariates include age, follow-up cycle, BMI, BMI at age 18 y (women) or 21 y (men), ethnicity, physical activity, smoking status, pack-years of smoking, history of hypertension, history of hypercholesterolemia, history of diabetes, family history of cancer, family history of diabetes, family history of myocardial infarction, current multivitamin use, regular aspirin use, menopausal status and hormone use in women, total caloric intake, alcohol consumption, glycemic load, and intakes of unprocessed red meat, processed meat, nuts, fruits, vegetables, total calcium, and total fiber.

Ascertainment of death

Deaths were identified from state statistics records, the National Death Index, next of kin, and the postal system. Both cohorts ascertained deaths with >96% completeness (16). Cause of death was determined from review of medical records by physicians or from death certificates. In our analysis, the primary endpoint was all-cause mortality. Secondary endpoints included CVD mortality (International Classification of Diseases, Eighth Revision, codes 390–458) and cancer mortality (codes 140–207).

Statistical analysis

We used time-varying Cox proportional hazards regression models with age as the timescale to estimate HRs and 95% CIs for mortality across increasing categories of yogurt intake. Participants were followed prospectively from their age in months at the return date of the baseline SFFQ (1980 for the NHS and 1986 for the HPFS) until their age in months at the date of death, loss to follow-up, or end of follow-up (1 June, 2012 for the NHS and 31 January, 2012 for the HPFS), whichever came first. We calculated the cumulative average of food intakes from baseline to the last questionnaire before censoring events in order to minimize within-person variation and to best reflect long-term dietary intake (17). In the multivariable analysis, we entered height (in inches, quintiles), BMI (in kg/m^2) (<22, 22–24, 24–25, 25–27, 27–29, 29–30, 30–32, 32–35, 35–40, or ≥40), BMI at age 18 (women) or 21 (men) (<19, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, ≥30), ethnicity (whites, nonwhites), physical activity (<3, 3–9, 9–18, 18–27, or ≥27 metabolic equivalent-h/wk), smoking status [never, past, or current (1–14 or ≥15 cigarettes/d)], pack-years of smoking (in women: ≤15, 16–25, 26–45, and ≥46; in men: <10, 11–24, 25–44, and ≥45), history of hypertension (yes, no), history of hypercholesterolemia (yes, no), history of diabetes (yes, no), family history of cancer (yes, no), family history of diabetes (yes, no), family history of myocardial infarction (yes, no), current multivitamin use (yes, no), regular aspirin use (≥2 tablets/wk, <2 tablets/wk), menopausal status and hormone use (premenopausal, and never, past, and current users of postmenopausal hormone) in women, total caloric intake (quintiles), alcohol consumption (<5, 5–10, 10–15, 15–30, or ≥30 g/d), glycemic load (quintiles), and intakes of unprocessed red meat, processed meat, nuts, fruits, vegetables, total calcium, and total fiber (all in quintiles). Because yogurt consumption may reduce weight and therefore represent an intermediate variable with regards to the yogurt intake and mortality relation, we excluded BMI from the model in a sensitivity analysis.

In sensitivity analyses, we stopped updating dietary information (18) when a participant reported a diagnosis of cancer (except nonmelanoma skin cancer), CVD, or diabetes, because these conditions may lead to dietary change. We performed stratified analyses by age, BMI, and smoking, and evaluated the interaction using a likelihood ratio test.

We further estimated the associations with all-cause mortality for substituting 1 serving of any of several alternative foods, including red meat (85 g), processed meat (28–45 g), nuts (28 g), whole grains (28 g), cheese (1 oz, 1 slice, or $\frac{1}{2}$ cup), milk (8 oz), or total other dairy foods, for yogurt. The variable "other dairy foods" consisted of the sums of skim milk, whole milk, dairy-cottage or ricotta cheese, dairy cream cheese, dairy cream, sour cream, ice cream, sherbet, and butter.

We chose dairy food alternatives (e.g., cheese, milk) and foods which are also important providers of protein and we explored some foods considered healthy (e.g., nuts, whole grain) and some foods considered unhealthy (e.g., red and processed meat) for the substitution.

To calculate the substitutional effect, we included the yogurt variable and the alternative food variable red meat, processed meat, nuts, whole grains, cheese, milk, and total other dairy products as continuous variables in the same multivariable model that in addition included nondietary covariates and total energy intake. The difference in their β-coefficients, as well as their variances and covariance, were used to estimate the effect size for the substitution associations. The proportional hazards assumption was tested by adding interaction terms between yogurt intake and follow-up time to the Cox proportional model (P-interaction > 0.05). All statistical tests were 2-sided and P values were considered statistically significant at the 5% level. Analyses were performed using SAS version 9.4 (SAS Institute Inc.).

Results

During 3,354,957 person-years of follow-up, 33,228 deaths from any cause (women = 20,831, men = 12,397) were ascertained, of which 7940 were due to CVD (women = 4207, men = 3733) and 11,985 (women = 7985, men = 4000) were due to cancer. During each questionnaire cycle, yogurt intake was higher in women than in men and increased in both sexes during follow-up (data not shown). Characteristics of the study cohorts according to ascending categories of yogurt intake are summarized in **Tables 1** and **2**. Compared with women and men with a lower frequency of yogurt intake, those with greater yogurt intake were less likely to currently smoke and to consume red and processed meat and alcohol and were more likely to be physically active and to consume fruits and vegetables. The analyses were conducted separately in each cohort because significant heterogeneity was detected in the results from the 2 cohorts. Among women, compared with no yogurt consumption, regular yogurt intake was inversely related to all-cause mortality in the age-adjusted model (HR: 0.66; 95% CI: 0.62, 0.71; P-trend < 0.001) (**Table 3**). After additional control for demographic, diet, lifestyle, and other cardiometabolic risk factors, the HRs of mortality were 0.89 (95% CI: 0.86, 0.93) for ≤1–3 servings/mo, 0.85 (95% CI: 0.81, 0.89) for 1 serving/wk, 0.88 (95% CI: 0.84, 0.91) for 2–4 servings/wk, and 0.91 (95% CI: 0.85, 0.98) for >4 servings/wk in women, although the P for trend was not statistically significant (P-trend = 0.34). We found an inverse association between greater yogurt intake and all-cause mortality in the age-adjusted model among men (age-adjusted HR for comparison of extreme categories: 0.84; 95% CI: 0.76, 0.92), which was attenuated and no longer statistically significant after adjustment for other covariates (multivariable-adjusted HR: 1.05; 95% CI: 0.95, 1.16; P-trend = 0.70).

On evaluation of cause-specific mortality, high compared with low yogurt intake was statistically significantly inversely related to cancer mortality (multivariable-adjusted HR: 0.87; 95% CI: 0.78, 0.98; P-trend = 0.04) in women (Table 3). For CVD mortality, a statistically significant inverse association was found in both sexes in the age-adjusted model, but that association was attenuated after accounting for other covariates.

Exclusion of BMI from the models did not essentially alter the results (data not shown). In further sensitivity analyses, where diet was no longer updated at diagnosis of an intermediate event (e.g., CVD, cancer, or diabetes), the inverse associations for all-cause mortality and CVD mortality were stronger than in the initial analysis in both sexes (**Supplemental Table 1**). There were no significant differences in the associations between yogurt

TABLE 1 Age-standardized characteristics of the 82,348 women in the Nurses' Health Study included in this study according to yogurt consumption during follow-up[1]

	Yogurt consumption, servings				
Characteristics	Never	>0 to ≤1–3/mo	1/wk	2–4/wk	>4/wk
Person-years	832,281	630,767	282,556	546,616	133,981
Mean age, y	57.2 ± 11.3	60.3 ± 11.3	62.1 ± 11.4	62.8 ± 10.4	62.1 ± 10.7
Height, in	64.4 ± 2.4	64.5 ± 2.4	64.6 ± 2.4	64.6 ± 2.4	64.7 ± 2.5
BMI, kg/m^2	25.2 ± 4.7	25.5 ± 4.7	25.4 ± 4.6	25.3 ± 4.5	24.8 ± 4.4
BMI at age 18, kg/m^2	21.2 ± 3.0	21.3 ± 2.9	21.3 ± 2.9	21.4 ± 2.9	21.4 ± 3.0
Current smoker	22.2	13.3	10.3	9.3	9.4
White	97.7	97.1	97.6	97.7	97.2
Physical activity, MET-h/wk	13.8 ± 16.7	15.4 ± 17.7	16.8 ± 17.0	18.5 ± 18.6	21.9 ± 22.7
History of hypertension	38.4	40.5	40.4	39.7	36.4
History of hypercholesterolemia	36.8	44.3	45.9	45.9	41.3
Family history of diabetes	28.0	28.9	28.4	28.2	27.4
Family history of myocardial infarction	26.0	26.2	25.4	25.4	25.1
Family history of cancer	13.8	13.7	13.9	13.1	13.4
Postmenopausal	69.3	73.2	74.1	75.6	75.2
Current postmenopausal hormone use	46.1	48.6	47.7	48.4	48.0
Multivitamin use	41.7	50.0	55.8	57.4	60.4
Aspirin use	41.4	41.2	40.9	42.0	41.7
Mean dietary intake					
Total energy intake, kcal/d	1615 ± 455	1639 ± 425	1690 ± 426	1752 ± 422	1873 ± 445
Alcohol, g/d	6.7 ± 10.8	5.9 ± 9.0	5.7 ± 8.3	5.6 ± 7.9	5.5 ± 7.8
Red meat consumption, servings/d	0.6 ± 0.4	0.5 ± 0.4	0.5 ± 0.4	0.5 ± 0.4	0.4 ± 0.4
Processed meat consumption, servings/d	0.3 ± 0.3	0.3 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.2
Fruit intake, servings/d	2.0 ± 1.2	2.1 ± 1.1	2.3 ± 1.1	2.5 ± 1.2	3.0 ± 1.5
Vegetable intake, servings/d	2.5 ± 1.3	2.7 ± 1.3	2.9 ± 1.3	3.1 ± 1.4	3.4 ± 1.7
Fiber intake, g/d	14.9 ± 4.9	16.3 ± 4.6	17.0 ± 4.5	17.5 ± 4.5	18.2 ± 5.1
Nut intake, servings/d	0.1 ± 0.3	0.1 ± 0.2	0.2 ± 0.3	0.2 ± 0.2	0.2 ± 0.3
Glycemic load	94.7 ± 22.0	96.8 ± 18.7	97.7 ± 17.5	99.0 ± 16.2	98.8 ± 16.5
Calcium, mg/d	801.9 ± 329.9	905.4 ± 333.1	974.2 ± 333.8	1050.4 ± 330.5	1187.2 ± 341.5

[1] Values are means ± SDs or percentages and are standardized to the age distribution of the study population (except age). Updated information throughout follow-up was used to calculate the mean for continuous variables and percentage for categorical variables. MET, metabolic equivalent of task.

consumption and risk of all-cause mortality according to strata of age, BMI, and pack-years of smoking (**Table 4**). To test further the robustness of the results, we chose a different reference group (e.g., low/occasional consumers) and the results did not appreciably change.

In the substitution analyses, replacing 1 serving/d of yogurt with 1 serving/d of nuts (men and women) or whole grains (women only) was related to a reduced all-cause mortality risk (**Table 5**). Substitution of red meat, processed meat (men and women), and milk or other dairy foods (women) for yogurt was related to a greater mortality risk.

Discussion

We observed an inverse association of regular yogurt consumption with all-cause mortality and mortality from cancer in women, but these associations were attenuated in the multivariable-adjusted model and did not show a clear mortality trend for increasing yogurt consumption. We further noted an inverse association for cancer mortality; an inverse association for CVD mortality vanished after multivariable adjustment. Our results showed no indication for a relation of regular yogurt consumption to mortality among men. Substitution of 1 serving/d of nuts (men and women) or whole grains (women) for 1 serving/d of yogurt was associated with a reduced risk of all-cause mortality. Replacing yogurt with red meat, processed meat (men and women), and milk or total other dairy foods (women) was associated with a greater all-cause mortality risk.

Available data from prospective studies provided inconsistent results concerning the role of yogurt consumption in mortality risk. Whereas a nonsignificant inverse association between yogurt intake and all-cause mortality was found among men and women in the Whitehall II cohort (multivariable-adjusted HR: 0.74; 95% CI: 0.53, 1.05) (19) and European Investigation into Cancer and Nutrition cohort—Netherlands (HR: 0.95; 95% CI: 0.85, 1.07) (20), a nonsignificant positive association with mortality comparing the highest with the lowest category of yogurt intake was reported in a community-based cohort in Australia (HR: 1.22; 95% CI: 0.77, 1.93) (21). A recent cohort study in Iran (22) reported an 11% lower risk of all-cause mortality (multivariable-adjusted HR: 0.89; 95% CI: 0.79, 1.00) and a 16% lower risk of CVD mortality (HR: 0.84; 95% CI: 0.70, 1.00) associated with the highest quintile of yogurt intake. However, the aforementioned studies did not provide risk estimates for men and women separately. Findings from the Netherlands Cohort Study (23) revealed a borderline significant inverse association between yogurt consumption and all-cause-mortality in men (HR: 0.96; 95% CI: 0.92, 1.00) but not in women (HR: 1.00; 95% CI: 0.95, 1.05). Reasons for apparently inconsistent findings among studies regarding the relation of

TABLE 2 Age-standardized characteristics of 40,278 men in the Health Professionals Follow-Up Study included in this study according to yogurt consumption during follow-up[1]

	Yogurt consumption, servings				
Characteristics	Never	>0 to ≤1–3/mo	1/wk	2–4/wk	>4/wk
Person-years	421,654	244,228	84,800	138,975	39,407
Mean age, y	62.4 ± 11.2	62.9 ± 11.0	63.1 ± 11.2	64.7 ± 10.8	63.7 ± 11.1
Height, in	70.2 ± 2.8	70.23 ± 2.8	70.2 ± 2.9	70.3 ± 2.8	70.3 ± 2.8
Current BMI, kg/m^2	25.8 ± 3.4	25.9 ± 3.4	25.8 ± 3.6	25.7 ± 3.4	25.1 ± 3.3
BMI at age 21 y, kg/m^2	22.9 ± 2.9	23.2 ± 2.9	23.2 ± 3.0	23.3 ± 2.9	23.1 ± 2.8
Current smoker	8.0	3.9	3.0	2.7	1.9
White	94.9	94.9	95.9	95.3	94.8
Physical activity, MET-h/wk	27.4 ± 27.2	31.4 ± 28.6	34.0 ± 29.9	36.1 ± 30.2	39.9 ± 34.6
History of hypertension	36.3	38.0	37.6	38.3	36.2
History of hypercholesterolemia	38.5	45.9	46.1	47.3	42.0
Family history of diabetes	13.3	15.0	14.2	15.6	14.5
Family history of myocardial infarction	35.3	35.1	35.0	36.2	35.8
Family history of cancer	34.3	34.7	34.9	36.5	34.3
Multivitamin use	40.6	48.7	52.8	56.8	57.6
Aspirin use	37.8	40.5	40.5	43.0	39.3
Mean dietary intake					
Total energy intake, kcal/d	1940.4 ± 559.7	1948.1 ± 536.1	2034.8 ± 542.3	2076.1 ± 539.6	2232.8 ± 590.4
Alcohol, g/d	12.2 ± 15.5	10.4 ± 12.9	10.0 ± 12.0	9.7 ± 11.6	8.9 ± 10.9
Red meat consumption, servings/d	0.6 ± 0.5	0.5 ± 0.4	0.5 ± 0.4	0.5 ± 0.4	0.4 ± 0.4
Processed meat consumption, servings/d	0.4 ± 0.4	0.3 ± 0.4	0.3 ± 0.3	0.2 ± 0.3	0.2 ± 0.3
Fruit intake, servings/d	2.1 ± 1.4	2.5 ± 1.5	2.7 ± 1.4	3.0 ± 1.5	3.6 ± 1.9
Vegetable intake, servings/d	2.8 ± 1.6	3.2 ± 1.6	3.3 ± 1.7	3.5 ± 1.7	3.8 ± 2.0
Fiber intake, g/d	20.5 ± 6.4	22.4 ± 6.2	23.1 ± 6.0	23.9 ± 6.4	24.8 ± 6.9
Nuts intake, servings/d	0.2 ± 0.4	0.3 ± 0.4	0.3 ± 0.4	0.3 ± 0.4	0.3 ± 0.5
Glycemic load	125.2 ± 24.6	129.8 ± 22.1	131.8 ± 20.7	133.9 ± 20.4	136.6 ± 20.9
Calcium, mg/d	860.4 ± 367.4	931.2 ± 358.9	979.8 ± 350.6	1051.3 ± 349.3	1210.9 ± 378.5

[1] Values are means ± SDs or percentages and are standardized to the age distribution of the study population (except age). Updated information throughout follow-up was used to calculate the mean for continuous variables and percentage for categorical variables. MET, metabolic equivalent of task.

yogurt consumption to mortality may include variations in the exposure range, type of yogurt consumed, bacterial strains in the yogurt, dietary assessment methods, and general dietary pattern among the subjects; the inclusion of different confounding variables in the models; residual confounding; or study size.

We estimated the effects of replacing yogurt with other foods on mortality and found that replacing yogurt with nuts or whole grains was related with lower all-cause mortality in women, whereas replacing yogurt with red meat, processed meat, milk, or other dairy foods was related to a greater mortality risk. Among men, replacing yogurt with nuts appeared to lower mortality risk, whereas replacing yogurt with red meat or unprocessed meat was related to a higher mortality risk. These findings provide important information on healthier or unhealthier food alternatives suggesting that yogurt may represent a better food choice over other dairy products in women.

Although frequent yogurt consumption is correlated with higher intake of calcium (Tables 1, 2), the inverse association between yogurt consumption and mortality was not substantially affected by adjustment for calcium intake. By adjusting our analyses for calcium intake we aimed to isolate the association between yogurt consumption and mortality not due to calcium.

Potential biological mechanisms explaining an inverse association between yogurt consumption and mortality may pertain to alterations in the gut microbiome. In a healthy individual, the gut microflora influences intestinal homeostasis by stimulating the innate and adaptive immune system, which may link intestinal microbiota changes to gut health and immune system–related diseases in humans (3, 24). Lactic acid bacteria in the intestine can suppress the growth of pathogenic microbiota, thereby reducing infection and increasing anticarcinogenic effects (25, 26). In experimental studies, regular consumption of fermented yogurt products increased high-density cholesterol concentrations (27) and decreased total cholesterol and low-density cholesterol (28). Food-ingested bacteria may synthesize vitamin K-2 (menaquinone) (29), which increases insulin sensitivity (30). Further, randomized controlled trials suggest a role in chronic inflammation (31, 32) attributed to yogurt and other dairy products. In a previous investigation in the NHS and HPFS (33), greater yogurt consumption was found to be associated with less weight gain, supporting emerging evidence that changes in intestinal bacteria may influence weight gain. Regular consumption of fermented dairy products may provide a more favorable oxidative stress and inflammatory marker profile than nonfermented milk (34), the latter of which has shown no consistent relation with mortality (35). During fermentation, changes in yogurt composition occur that may include an increase in free fatty acid, peptide, free amino acid, folic acid, and choline contents, and bioavailability of calcium, and a decrease in vitamins B-6 and B-12 and lactose (4). Some of these composition changes may also contribute to the association with lower mortality. In particular, high calcium and also high folate concentrations have been associated with a reduced risk of colorectal cancer incidence and mortality.

TABLE 3 Association between yogurt consumption and mortality in 82,348 participants of the Nurses' Health Study and 40,278 participants of the Health Professionals Follow-Up Study between 1980 and 2012 (women) and 1986 and 2012 (men)[1]

	Yogurt consumption, servings					
	Never	>0 to ≤1–3/mo	1/wk	2–4/wk	>4/wk	*P*-trend
All-cause mortality						
Women						
Cases/person-years	7013/832,189	5395/630,665	2506/282,535	4800/546,544	1117/133,960	
Age-adjusted HR (95% CI)	1 (ref)	0.75 (0.72, 0.78)	0.66 (0.63, 0.70)	0.66 (0.64, 0.69)	0.66 (0.62, 0.71)	<0.001
Multivariate-adjusted HR (95% CI)	1 (ref)	0.89 (0.86, 0.93)	0.85 (0.81, 0.89)	0.88 (0.84, 0.91)	0.91 (0.85, 0.98)	0.34
Men						
Cases/person-years	5941/421,654	2917/244,228	1002/84,800	2005/138,975	532/39,407	
Age-adjusted HR (95% CI)	1 (ref)	0.82 (0.79, 0.86)	0.77 (0.72, 0.83)	0.83 (0.79, 0.87)	0.84 (0.76, 0.92)	<0.001
Multivariate-adjusted HR (95% CI)	1 (ref)	0.99 (0.94, 1.03)	0.98 (0.91, 1.05)	1.04 (0.98, 1.10)	1.05 (0.95, 1.16)	0.70
CVD mortality						
Women						
Cases	1472/837,258	1127/634,560	472/284,372	925/550,095	211/134,767	
Age-adjusted HR (95% CI)	1 (ref)	0.75 (0.70, 0.82)	0.62 (0.56, 0.69)	0.64 (0.59, 0.70)	0.63 (0.55, 0.73)	<0.001
Multivariate-adjusted HR (95% CI)	1 (ref)	0.88 (0.81, 0.96)	0.78 (0.70, 0.87)	0.86 (0.78, 0.94)	0.92 (0.79, 1.08)	0.41
Men						
Cases	1795/425,569	874/246,199	319/85,436	592/140,304	153/39,750	
Age-adjusted HR (95% CI)	1 (ref)	0.83 (0.77, 0.91)	0.84 (0.74, 0.95)	0.81 (0.73, 0.89)	0.80 (0.68, 0.95)	0.004
Multivariate-adjusted HR (95% CI)	1 (ref)	0.96 (0.88, 1.05)	1.02 (0.90, 1.16)	0.97 (0.88, 1.08)	0.95 (0.79, 1.13)	0.19
Cancer mortality						
Women						
Cases	2738/836,077	2040/633,706	998/283,882	1812/549,218	397/134,602	
Age-adjusted HR (95% CI)	1 (ref)	0.78 (0.73, 0.82)	0.77 (0.71, 0.82)	0.70 (0.66, 0.75)	0.66 (0.59, 0.73)	<0.001
Multivariate-adjusted HR (95% CI)	1 (ref)	0.91 (0.86, 0.96)	0.94 (0.87, 1.02)	0.91 (0.85, 0.97)	0.87 (0.78, 0.98)	0.04
Men						
Cases	1938/425,416	975/246,084	315/85,443	598/140,301	174/39,730	
Age-adjusted HR (95% CI)	1 (ref)	0.84 (0.77, 0.90)	0.76 (0.67, 0.86)	0.78 (0.71, 0.86)	0.86 (0.73, 1.01)	0.03
Multivariate-adjusted HR (95% CI)	1 (ref)	1.00 (0.92, 1.08)	0.96 (0.85, 1.09)	0.98 (0.89, 1.09)	1.10 (0.93, 1.30)	0.42

[1]Multivariable Cox regression models adjusted for age, 2-y follow-up cycle, height (in inches) (quintiles), current BMI (in kg/m^2) (<22, 22–24, 24–25, 25–27, 27–29, 29–30, 30–32, 32–35, 35–40, or ≥40), BMI at age 18 y (women) or 21 y (men) (<19, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, ≥30), ethnicity (whites, nonwhites), physical activity (<3, 3–9, 9–18, 18–27, or ≥27 metabolic equivalent-h/wk), smoking status [never, past, or current (1–14 or ≥15 cigarettes/d)], pack-years of smoking (in women: ≤15, 16–25, 26–45, and ≥46; in men: <10, 11–24, 25–44, and ≥45), history of hypertension (yes, no), history of hypercholesterolemia (yes, no), history of diabetes (yes, no), family history of cancer (yes, no), family history of diabetes (yes, no), family history of myocardial infarction (yes, no), current multivitamin use (yes, no), regular aspirin use (≥2 tablets/wk, <2 tablets/wk), menopausal status and hormone use in women (premenopausal, and never, past, and current users of postmenopausal hormone), total caloric intake (quintiles), alcohol consumption (<5, 5–10, 10–15, 15–30, or ≥30 g/d), glycemic load (quintiles), and intakes of unprocessed red meat, processed meat, nuts, total fiber, fruits, vegetables, and total calcium (all in quintiles).

Whether there are biological reasons for the statistically inverse association between yogurt consumption and mortality in the multivariable-adjusted analysis in women but not men requires further investigation. Although some studies reported differences in gut microbial composition between the sexes (36, 37), other studies suggested that sex has no or very limited impact on intestinal microbiota (38, 39). A recent cross-sectional study among 293 Japanese young adults (40) posited that yogurt consumption may differently affect intestinal microbiota in women and men. In that study, women had higher counts of total bacteria, *Bifidobacterium*, and *Lactobacillus gasseri* subgroup, and lower concentrations of SCFAs in the fecal microbiota, than men (40). Yogurt consumption was positively correlated with increased *Lactobacillus casei* and succinic acid in women and inversely correlated with *L. sakei,* Enterobacteriaceae, and *Staphylococcus* in men (40). Intriguing evidence suggests that the commensal microbial community may alter sex hormone concentrations (41–43). Some residual confounding arising from measurement error in covariates or modeling of covariates is a potential concern. Although the association between yogurt consumption and all-cause mortality among women persisted after adjusting for other foods which were unequally distributed between women who regularly consumed yogurt and those who did not, a clear dose-response association with mortality was lacking.

Particular strengths of our study include the large sample size, its prospective design, and the ability to address the impact of potential confounding. The use of repeated measures of yogurt consumption may have reduced the potential for exposure misclassification error. In comparison with previous studies, we assessed the associations using repeated measures of diet over a long follow-up period, which might be particularly important considering trends of increasing yogurt consumption over time as seen in our results. Moreover, the large number of deaths further allowed us to conduct analyses on cause-specific mortality. Our study is also unique in the evaluation of substitution effects, which estimates the health effects by taking into account an alternative food. Several potential limitations need to be acknowledged. Although our validation studies have demonstrated high validity of yogurt intake by

TABLE 4 Multivariable-adjusted HRs and 95% CIs for the association between yogurt consumption and all-cause mortality, stratified by age, BMI, and smoking, in the Nurses' Health Study and Health Professionals Follow-Up Study[1]

	Yogurt consumption, servings					
	Never	>0 to ≤1–3/mo	1/wk	2–4/wk	>4/wk	*P*-interaction
Women						
Age, y						
<60 ($n = 4660$)	1 (ref)	0.93 (0.86, 1.00)	0.88 (0.79, 0.98)	0.91 (0.83, 0.99)	0.93 (0.80, 1.07)	0.81
≥60 ($n = 16,171$)	1 (ref)	0.89 (0.85, 0.92)	0.84 (0.80, 0.89)	0.87 (0.83, 0.91)	0.91 (0.84, 0.98)	
BMI, kg/m^2						
<25 ($n = 10,499$)	1 (ref)	0.80 (0.76, 0.84)	0.78 (0.73, 0.83)	0.78 (0.74, 0.83)	0.84 (0.77, 0.92)	0.15
≥25 ($n = 10,308$)	1 (ref)	0.89 (0.85, 0.94)	0.82 (0.76, 0.87)	0.88 (0.83, 0.93)	0.92 (0.83, 1.02)	
Smoking						
Never smoker ($n = 6780$)	1 (ref)	0.91 (0.85, 0.97)	0.87 (0.80, 0.95)	0.91 (0.84, 0.97)	0.88 (0.78, 1.00)	0.07
>0 to <10 pack-years of smoking ($n = 2285$)	1 (ref)	0.97 (0.85, 1.09)	0.94 (0.81, 1.10)	0.97 (0.85, 1.10)	0.97 (0.79, 1.18)	
≥10 pack-years of smoking ($n = 10,477$)	1 (ref)	0.85 (0.81, 0.90)	0.78 (0.73, 0.83)	0.81 (0.76, 0.85)	0.88 (0.80, 0.97)	
Men						
Age, y						
<60 ($n = 827$)	1 (ref)	0.99 (0.82, 1.18)	1.10 (0.84, 1.44)	1.28 (1.02, 1.61)	1.16 (0.80, 1.69)	0.11
≥60 ($n = 11,570$)	1 (ref)	0.98 (0.94, 1.03)	0.97 (0.90, 1.05)	1.02 (0.97, 1.09)	1.04 (0.94, 1.15)	
BMI, kg/m^2						
<25 ($n = 5719$)	1 (ref)	0.97 (0.90, 1.04)	0.97 (0.87, 1.08)	1.03 (0.94, 1.12)	1.17 (1.02, 1.34)	0.64
≥25 ($n = 6647$)	1 (ref)	1.01 (0.95, 1.08)	1.00 (0.90, 1.10)	1.07 (0.99, 1.15)	0.93 (0.81, 1.08)	
Smoking						
Never smoker ($n = 4511$)	1 (ref)	0.96 (0.89, 1.04)	0.94 (0.83, 1.05)	1.04 (0.95, 1.14)	1.02 (0.88, 1.18)	0.28
>0 to <10 pack-years of smoking ($n = 954$)	1 (ref)	0.81 (0.66, 0.99)	0.84 (0.64, 1.11)	0.95 (0.76, 1.20)	0.86 (0.60, 1.24)	
≥10 pack-years of smoking ($n = 6261$)	1 (ref)	0.92 (0.86, 0.98)	0.87 (0.78, 0.97)	0.93 (0.85, 1.01)	0.91 (0.77, 1.06)	

[1]Multivariable Cox regression models adjusted for age, 2-y follow-up cycle, height (in inches) (quintiles), current BMI (in kg/m^2) (<22, 22–24, 24–25, 25–27, 27–29, 29–30, 30–32, 32–35, 35–40, or ≥40), BMI at age 18 y (women) or 21 y (men) (<19, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, ≥30), ethnicity (whites, nonwhites), physical activity (<3, 3–9, 9–18, 18–27, or ≥27 metabolic equivalent-h/wk), smoking status [never, past, or current (1–14 or ≥15 cigarettes/d)], pack-years of smoking (in women: ≤15, 16–25, 26–45, and ≥46; in men: <10, 11–24, 25–44, and ≥45), history of hypertension (yes, no), history of hypercholesterolemia (yes, no), family history of cancer (yes, no), family history of diabetes (yes, no), family history of myocardial infarction (yes, no), current multivitamin use (yes, no), regular aspirin use (≥2 tablets/wk, <2 tablets/wk), menopausal status and hormone use in women (premenopausal, and never, past, and current users of postmenopausal hormones), total caloric intake (quintiles), alcohol consumption (<5, 5–10, 10–15, 15–30, or ≥30 g/d), glycemic load (quintiles), and intakes of unprocessed red meat, processed meat, nuts, total fiber, fruits, vegetables, and total calcium (all in quintiles) (where appropriate).

the SFFQs (11), measurement error resulting from self-report assessment is inevitable. We carefully controlled for potential confounding variables in the analysis, but as aforementioned, we cannot rule out the possibility of residual confounding or unmeasured confounding. Although yogurt products consumed in the United States mostly contain probiotic cultures of *Lactobacillus acidophilus*, *L. casei*, and *Bifidobacterium*, we lack information about the yogurt composition, in particular the species and concentration of probiotics, which further complicates the interpretation of our findings. Also, yogurt consumption in this population was not high enough to allow stratified analyses of different types of yogurt such as low-fat and fat-free yogurts or (artificially) sweetened yogurts. Consumption of yogurts fortified with additional probiotics was not assessed.

TABLE 5 HR and 95% CI of all-cause mortality associated with replacement of 1 serving/d of yogurt with 1 serving of other foods with 1 serving/d of other foods[1]

	Women	Men
Replacement with red meat	1.14 (1.05, 1.24)	1.16 (1.05, 1.29)
Replacement with processed meat	1.31 (1.20, 1.43)	1.16 (1.04, 1.28)
Replacement with nuts	0.73 (0.67, 0.79)	0.86 (0.78, 0.95)
Replacement with whole grains	0.86 (0.79, 0.94)	0.93 (0.84, 1.02)
Replacement with other dairy foods[2]	1.08 (0.99, 1.17)	1.05 (0.95, 1.16)
Replacement with milk	1.15 (1.05, 1.25)	1.06 (0.95, 1.17)
Replacement with cheese	1.01 (0.93, 1.10)	1.07 (0.97, 1.18)

[1]Multivariable Cox regression models adjusted for age, 2-y follow-up cycle, height (in inches) (quintiles), current BMI (in kg/m^2) (<22, 22–24, 24–25, 25–27, 27–29, 29–30, 30–32, 32–35, 35–40, or ≥40), BMI at age 18 y (women) or 21 y (men) (<19, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, ≥30), ethnicity (whites, nonwhites), physical activity (<3, 3–9, 9–18, 18–27, or ≥27 metabolic equivalent-h/wk), smoking status [never, past, or current (1–14 or ≥15 cigarettes/d)], pack-years of smoking (in women: ≤15, 16–25, 26–45, and ≥46; in men: <10, 11–24, 25–44, and ≥45), history of hypertension (yes, no), history of hypercholesterolemia (yes, no), history of diabetes (yes, no), family history of cancer (yes, no), family history of diabetes (yes, no), family history of myocardial infarction (yes, no), current multivitamin use (yes, no), regular aspirin use (≥2 tablets/wk, <2 tablets/wk), menopausal status and hormone use in women (premenopausal, and never, past, and current users of postmenopausal hormone), total caloric intake (quintiles), and alcohol consumption (<5, 5–10, 10–15, 15–30, or ≥30 g/d).

[2]Other dairy foods consisted of the sums of skim milk, whole milk, dairy-cottage or ricotta cheese, dairy cream cheese, dairy cream, sour cream, ice cream, sherbet, and butter.

In conclusion, we found an inverse association between regular yogurt consumption and all-cause mortality and mortality from cancer in women. Given that no clear dose–response relation was apparent for mortality, this result must be interpreted with caution. Further, the effect may depend on the food that yogurt is substituted for. Future research is needed to confirm this finding and to determine whether yogurt consumption is associated with mortality among men.

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